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Patentanmeldung Nr. Patent application No. Demande de brevet n°

99116026.8

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Sanofi-Synthélabo
75013 Paris
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Titre de l'invention:
Use of monoamine oxydase inhibitors for the manufacture of drugs intended for the treatment of obesity

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USE OF MONOAMINE OXYDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

The present invention relates to the use of monoamine oxydase inhibitors in the manufacture of drugs intended for the treatment of obesity.

As described in Cheryl P.Kordik and Allen B.Reitz, *J. of Med. Chem.*, Vol 42(2), 181-201, reviewing the various known strategies to treat obesity, obesity is a "chronic condition characterized by overabundance of adipose tissue" which "correlates with risks such as high blood pressure, coronary heart disease, diabetes, altered steroid metabolism, gallstones and certain forms of cancer".

It has now been found that reversible selective inhibitors of monoamine oxydase A (MAO-A), reversible selective inhibitors of monoamine oxydase B (MAO-B) or reversible mixed inhibitors of monoamine oxydase A and B (MAO-B and MAO-A) have activity in decreasing body weight of obese patients.

Accordingly the present invention relates to the use of reversible selective inhibitors of monoamine oxydase A (MAO-A), reversible selective inhibitors of monoamine oxydase B (MAO-B) or reversible mixed inhibitors of monoamine oxydase A and B (MAO-A and MAO-B) for the manufacture of drugs intended for the treatment of obesity.

The invention therefore further relates to a method of treating obesity by administering to a patient in need of such treatment a therapeutically effective amount of a reversible selective inhibitor of monoamine oxydase A, a reversible selective inhibitor of monoamine oxydase B or a reversible mixed inhibitor of monoamine oxydase A and B.

In fact patients who may be treated may be men and women suffering from obesity or overw ight.

high affinity for the A isoform (MAO-A) and great selectivity versus the B isoform (MAO-B), which does not affect reuptake of noradrenaline (NA), serotonine (5-HT) or dopamine (DA).
Its chemical synthesis is described in EP 424244.

As reversible MAO-B inhibitor (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one is preferred.

As reversible mixed inhibitor of monoamine oxydase A and B [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one are preferred.

The active substance according to the invention can be administred to patients in a variety of pharmaceutical forms well-known in the art and particularly in the form of compositions formulated for administration by the oral, injectable, transdermal or rectal route.
For oral administration, said compositions can take the form of tablets, dragees or capsules prepared by the conventional techniques using known carriers and excipients, such as binding agents, fillers, lubricants and desintegration agents; they can also be in form of solutions, syrups or suspensions.
For administration by the injectable route, the compositions according to the invention may be in the form of injectable solutions, suspensions or emulsions containing an acceptable oily or aqueous liquid carrier.
For transdermal administration, the composition can take the form of a patch wherein the drug can be emcompassed in a gel, solution, ointment or cream.
For rectal administration, the compositions may be in the form of suppositories containing the conventional bases for suppositories.

The following examples relating to pharmacological data and a galenic formulation illustrate the present invention.

Example 1

FEEDING BEHAVIOUR IN FASTED RATS

Male Wistar rats (Iffa-Credo) were individually housed in polycarbonate cages (48x26.5x21.5 cm) in a temperature- and humidity-controlled animal colony room (20±2°C) with a 12-hour light dark cycle (7 a.m. - 7 p.m.). At least 1 week before the experiment, every animal was often handled and administered saline by oral route in order to avoid stress. Food and water were available ad libitum, and all testing was done in the home cage. Rats were fasted for 24 hour before testing and allowed free access to water. In the morning of the test day, rats were first assigned to either a treatment or a control group then weighed and administered drug or vehicle p.o. (10.30 a.m.) and returned to their home cage. Thirty minutes later, a measured quantity of food (RMM, Harlan Ibérica) was made available to the animals. The food intake is calculated every hour until 6 hours after the drug administration. (WO95/11894, Gehlert et al., *J. Pharmacol. Exp. Ther.*, 287, 122-127, 1998).
Grams of food consumed by the treated animals every hour was compared to food consumed by the control animals using one-way analysis of variance with a Newman-Keuls' test.

Table

Effect of befloxatone on food consumption during light period (7 a.m.-7 p.m.) in fasted rats (24 hours). Recording and access to food 11 a.m.-2 p.m.

Table

Effect of 7 days treatment with befloxatone (10 mg/kg/day, p.o.) on food consumption during dark period (4.30 p.m. - 4.30 a.m.) in fed male Wistar rats

Days of treatment	Food intake (g)	
	Control vehicle p.o. (n=7)	Befloxatone 10 mg/kg/day, p.o. (n=6)
1	3.98 ± 0.63	3.03 ± 0.40
2	5.91 ± 0.85	3.31 ± 1.00
3	7.95 ± 0.68	5.32 ± 0.69*
4	7.35 ± 0.57	6.12 ± 0.50
5	8.75 ± 0.76	6.10 ± 0.59*
6	9.69 ± 0.98	6.98 ± 0.61*
7	10.1 ± 0.74	6.95 ± 0.75*

*p< 0.05 vs control (ANOVA test)

These results show that in the model using **fasted rats**, befloxatone (3 mg/kg p.o.) inhibits food intake by about 25% during the first hour after administration of the drug, and in the model of **fed rats** with recording of food consumption in the dark, befloxatone (10 mg/kg p.o.), once a day for 7 days, inhibits as from the third day, food intake during the first four hours after drug administration.

claims

1. Use of a reversible selective inhibitor of monoamine oxydase A, reversible selective inhibitor of monoamine oxydase B or a reversible mixed inhibitor of monoamine oxydase A and B for the manufacture of a medicament intended for the treatment of obesity.

2. Use of a reverible mixed inhibitor of monoamine oxydase A and B according to claim 1.

3. The use according to claim 2 wherein the reversible mixed inhibitor of monoamine oxydase A and B is chosen among [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one.

4. Use of a reversible selective inhibitor of monoamine oxydase B according to claim 1.

5. The use according to claim 4 wherein the reversible selective monoamine oxydase B is chosen among lazabemide, milacemide, caroxazone and IFO.

6. The use according to claim 4 wherein the reverible selective monoamine oxydase B is (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one.

7. Use of a reversible selective inihibtor of monoamine oxydase A according to claim 1.

8. The use according to claim 7 wherein the reversible selective inhibitor of monoamine oxydase A is chosen among

USE OF MONOAMINE OXYDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

SANOFI-SYNTHELABO

Abstract :

The present invention relates to the use of reversible selective inhibitors of monoamine oxydase A (MAO-A), reversible selective inhibitors of monoamine oxydase B (MAO-B) or reversible mixed inhibitors of monoamine oxydase A and B (MAO-A and MAO-B) in the manufacture of drugs intended for the treatment of obesity.